

REMARKS

The Rejections Under 35 USC § 112 and The Claim Objection

Amendments were made to the form of claim 13, which render moot the section 112 rejections and the claim objection. The term “rapidly producing the freeze phrase from the elevated temperature” has been removed from claim 1, and was replaced with “lowering the temperature to freezing temperature to achieve lyophilization,” which is an equivalent thereof.

The Rejections Under 35 USC § 103

The Office Action admits that Gericke et al. does not teach the claimed process, i.e., the heating step before lyophilization. None of the cited references teaches or suggests the additional step of heating the solution to be lyophilized just prior to freezing said solution.

Contrary to the Office Action’s allegations, the additional heating step is not merely optimizing the temperature of the process or that of the shelf temperature. In a conventional freeze-drying process, the substance to be lyophilized is dissolved to form a solution by warming the solution if necessary. The solution is filtered and placed into a freeze dryer to be freeze dried. The cited prior art does not teach or suggest warming the solution after the solution is prepared and placed into the freeze dryer, but prior to freezing.

Franks teaches that the process cycle consists of four distinct stages: 1) freezing the solution, 2) primary drying, 3) secondary drying, and 4) removing the collected ice from the condenser. See Franks, page 225, second column. Nowhere does the prior art suggest or motivate an artisan to heat the solution after it is placed into the freeze dryer, but prior to the freezing step. Adding an entirely new untaught or un-suggested step into the process is more than mere optimization of the process. It would not have been obvious to one of skill in the art to even perform this step, and therefore not obvious to optimize this step, absent some teaching or motivation in the references to do so.

The Office Action alleges that the step of warming the solution to a certain temperature in the freeze dryer is seen to be a matter of optimizing the starting shelf temperature of the drying process by keeping the solution in a vial at about room temperature

(allegedly 30°C) for a while before lyophilization because such optimization is considered an optimization of a result effective variable. This allegation is unfounded for multiple reasons.

First, as discussed above, adding the new step of heating up the solution prior to lyophilization, but after the solution has been prepared and placed into the freeze dryer, is not merely the optimization of a result effective variable. No teaching or suggestion is present in any of the cited references for such a heating step.

Second, "room temperature" is not understood by those of skill in the art to be 30°C. Room temperature, according to Hawley's condensed Chemical Dictionary, 11th Ed., is "an ambient temperature from 20-25°C." Relevant page is attached.

Third, the Office Action has not established that warming the solution to a certain temperature after the solution has been prepared, but prior to lyophilization, would be equivalent to storing the solution at the alleged room temperature of 30°C (assuming for the moment that room temperature is 30°C). Nor does the Office Action establish that the final product of the alleged equivalent would be the same, i.e., a lyophilisate exhibiting improved dissolution rate that can be reconstituted in a particle-free manner, see specification on page 4, and Example 1. And even if equivalency could be established, that would not be adequate under law. The law requires that prior art references provide a specific teaching, suggestion or reason to provide the necessary motivation to one of skill in the art to perform the allegedly obvious step. No such specific teaching, suggestion or reason is provided in any of the references.

The Office Action then alleges that Franks teaches controlling shelf temperature for optimizing the results. Applicants respectfully disagree. Applicants believe that the Examiner is misreading the reference. The "shelf temperature" discussed as a process parameter in Franks refers to the temperature of the "shelves" during the freezing stage (stage 1) and during the primary and secondary drying phases (stages 2 and 3). See Franks, page 225, second column, the paragraph listing of the 4 stages of the process cycle (referring to shelves in the freezing and drying stages), and especially the paragraph following said outlining of the 4 stages discussing "shelf temperatures". Franks, as discussed above, does not even consider the starting shelf temperature (i.e., product temperature prior to process cycle) as part of the process cycle. See Franks, page 225, second column. Thus, Franks does not suggest the optimization of such product temperature prior to the process cycle.

Additionally, even if Franks would have taught that the temperature of the solution can be controlled prior to the process cycle, i.e., assuming for this argument that shelf temperature refers to starting shelf temperature, nowhere does Franks specifically teach or suggest any relationship between such shelf temperature and final product having amorphous properties and being reconstitutable in a particle free manner.

With respect to the product-by-process claims, to further clarify what was already believed inherently present, applicants amend the claims to specify that the product of the process is amorphous and reconstitutable in a particle free manner, and is thus patentably distinct from the product obtained by the prior art process. Support can be found, in Example 1, for example. Example 1a) demonstrates that the lyophilisate obtained by the claimed process results in an amorphous product and can be reconstituted in a particle-free manner, whereas comparative Example 1b) demonstrates in a side-by-side comparison that when the process is carried out in a conventional manner, i.e., without the heating step before lyophilization, but after the solution is prepared, the resultant product is crystalline that does not dissolve completely during reconstitution, i.e., not in a particle-free manner.

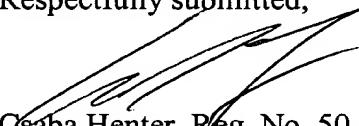
Furthermore, the claims of the present invention are directed to specific compounds, not specifically addressed by any of the references. The prior art only generally addresses lyophilization. No teaching or suggestion is present in any of the references that would motivate one of ordinary skill in the art to perform the claimed process on the claimed compounds.

Reconsideration is respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version With Markings To Show Changes Made**".

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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Version With Markings To Show Changes Made

In the Claims:

The claims have been amended as follows:

(Rapid?)

13. (Amended) A process for preparing a lyophilisate, having an improved dissolution rate, ^{while reducing residual insolubles} of 2-methyl-5-methylsulfonyl-4-(1-pyrrolyl)benzoylguanidine methanesulfonate, N-[2-methyl-4,5-bis-(methylsulfonyl)benzoyl]guanidine hydrochloride or 4-isopropyl-3-methylsulfonylbenzoylguanidine methanesulfonate, comprising dissolving 2-methyl-5-methylsulfonyl-4-(1-pyrrolyl)benzoylguanidine methanesulfonate, N-[2-methyl-4,5-bis-(methylsulfonyl)benzoyl]guanidine hydrochloride or 4-isopropyl-3-methylsulfonylbenzoylguanidine methanesulfonate to form a solution suitable for lyophilization by optionally warming the solution to accelerate dissolution, filtering the solution, placing the solution into a freeze drier in a vial, and then warming the solution to a temperature of 30°C to 95°C followed by rapidly producing lowering the temperature to freezing temperature to achieve lyophilization the freeze phrase from the elevated temperature.

26. (Amended) A lyophilisate of 2-methyl-5-methylsulfonyl-4-(1-pyrrolyl)benzoylguanidine methanesulfonate, N-[2-methyl-4,5-bis-(methylsulfonyl)benzoyl]guanidine hydrochloride or 4-isopropyl-3-methylsulfonylbenzoylguanidine methanesulfonate, that has been prepared by the process according to claim 13 and is amorphous and reconstitutable in a particle free manner.

28. (Amended) A lyophilisate of N-[2-methyl-4,5-bis-(methylsulfonyl)benzoyl]guanidine hydrochloride, that has been prepared by the process according to claim 13 and is amorphous and reconstitutable in a particle free manner.

29. (Amended) A lyophilisate of 2-methyl-5-methylsulfonyl-4-(1-pyrrolyl)benzoylguanidine methanesulfonate, that has been prepared by the process according to claim 13 and is amorphous and reconstitutable in a particle free manner.

30. (Amended) A lyophilisate of 4-isopropyl-3-methylsulfonylbenzoylguanidine methanesulfonate, that has been prepared by the process according to claim 13 and is amorphous and reconstitutable in a particle free manner.

(Rapid + complete)

Hawley's
Condensed Chemical
Dictionary

ELEVENTH EDITION

Revised by

N. Irving Sax

and

Richard J. Lewis, Sr.

1987



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rocket fuel. (rocket propellant). A substance or mixture that has the capacity for extremely rapid but controlled combustion, which produces large volumes of gas at high pressure and temperature. They may be either liquid, solid, or combinations of both. Liquid monopropellants are hydrogen peroxide and hydrazine, catalyzed by finely divided metals to decompose them into gases. Liquid bipropellants consist of the fuel and an oxidizer; typical fuels of this type are hydrogen, hydrazine, ammonia, and boron hydride, the oxidizers being oxygen, nitric acid, ozone, hydrogen peroxide, and water.

Solid propellants include nitrocellulose, plasticized with nitroglycerin or various phthalates; inorganic salts suspended in a plastic or synthetic rubber (e.g., "Thiokol") and containing a finely divided metal. The inorganic oxidizers used are ammonium and potassium nitrates and perchlorates.

Rockwell hardness. See hardness.

"**Rodar.**"¹⁵⁵ TM for an alloy composed of nickel 29%, cobalt 17%, manganese 0.30%, iron 53.7%.

Properties: Produces a permanent, vacuum-tight seal with simple oxidation procedure, resists mercury corrosion, readily machined and fabricated, can be welded, soldered, or brazed.

Forms: Wire, strip, bar.

Use: Sealing metal to hard glass.

rodenticide. A pesticide used to kill rats and other rodents.

See warfarin, squill.

"**Rodine.**"³⁴² TM for red squill liquid extract rodenticides.

rod mill. A closed steel cylinder one-third filled with rods of about the same length as the cylinder and 1-2 inches in diameter. As the cylinder rotates the rods roll over one another, exerting a combination of impact and grinding action on the charge. It gives a product of 50-60 mesh with a minimum of fines. Rod mills are used for pulp grinding in the paper industry and for size reduction of ores, minerals, metal powders, etc.

Roentgen, W. K. (1845-1923) A German physicist who discovered x-rays in 1895 for which he was awarded the Nobel Prize in 1901. Application of these to a number of important problems in analytical chemistry was developed by the Braggs, Moseley, von Laue, and Debye and Sherrer.

roentgen. (r). The international unit of quantity or dose for both x-rays and gamma rays. It is defined as the quantity of x- or gamma rays which will produce as a result of ionization one electrostatic unit of electricity of either sign in 1 cc (0.001293 g) of dry air as measured at 0C and standard atmospheric pressure. The use of the roentgen unit has been extended to include particle radiation such as alpha and beta particles and protons and neutrons.

See also rad, curie.

Rohrbach solution.

Properties: Clear, yellow liquid, very refractive, d 3.5.

Derivation: An aqueous solution of mercuric barium iodide.

Hazard: Toxic by ingestion and inhalation.

Use: Separating minerals by their specific gravity, microchemical detection of alkaloids.

roll mill. Two chilled steel rolls 48-72 inches wide and 12-24 inches in diameter, turning in opposite directions at different speeds to exert shearing action; the separation (or nip) is adjustable by set screws. As the shearing friction generates considerable heat, the rolls are water-cooled. Such mills are standard equipment in the rubber, plastic and adhesives industries, several usually rotating on one shaft. They can be used for mixing, but their chief use is for prewarming calender and extruder feed. Mills with three rolls are used for mixing and grinding paints and printing inks. Laboratory sizes of all types are available.

"**Romark.**"⁴⁴⁸ TM for alkyd and chlorinated rubber type road-marking paints.

RON. Abbreviation for Research octane number.

ronnell. (O,O-dimethyl-O-(2,4,5-trichlorophenyl)phosphorothioate). CAS: 299-84-3.
 $(CH_3O)_2P(S)OC_6H_2Cl_3$.

Properties: Powder or granules, mp 41C, insoluble in water, soluble in most organic solvents.

Hazard: Toxic by ingestion and inhalation. Cholinesterase inhibitor, use may be restricted. TLV: 10 mg/m³ of air.

Use: Insecticide.

room temperature. An ambient temperature from 20-25C (68-77F).

rosaniline. CAS: 632-99-5.

$HOC(C_6H_4NH_2)_2C_6H_3(CH_3)NH_2$. A triphenylmethane dye.

Properties: Reddish-brown crystals, mp 186C (decomposes), soluble in acids and alcohol, slightly soluble in water.